Gene's role in attaining and maintaining muscle mass revealed in new study

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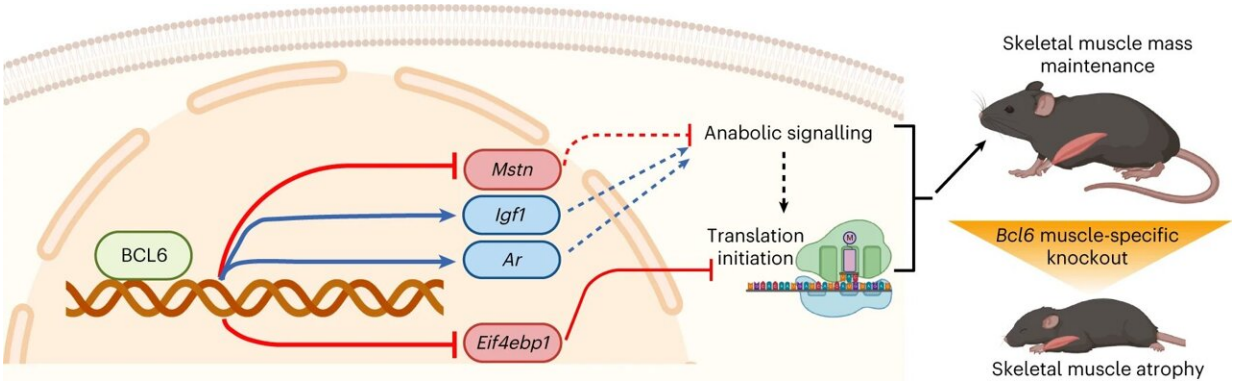

Model for BCL6-mediated control of skeletal muscle proteostasis. BCL6-mediated transcriptional regulation controls the expression of atrogenic regulators to establish and maintain skeletal muscle mass. BCL6 directly represses *Eif4ebp1* and possibly *Mstn*, while it directly activates *Igf1* and *Ar*. Loss of *Bcl6* in muscle acutely reduces cap-dependent translation and anabolic signaling, resulting in reduced protein synthesis, increased autophagy and skeletal muscle atrophy. Credit: *Nature Metabolism* (2024). DOI: 10.1038/s42255-024-00983-3

New research from Northwestern University has uncovered a previously unexplored relationship between a gene critical to immune cells and the establishment and maintenance of skeletal muscle mass and strength in mice.

The BCL6 gene has been known to play a key role in the function of immune cells and the body's inflammatory response. For decades, scientists have also known that the gene is expressed heavily in skeletal tissue, but until now, its function in this metabolic tissue was unknown.

"Usually when genes are expressed at high levels, it implies important function," said last author Dr. Grant D. Barish. "The study was undertaken with the idea the gene was doing something important in skeletal tissue, but we didn't know what."

Barish is the Martha Leland Sherwin Professor of Medicine in the endocrinology division at Northwestern University Feinberg School of Medicine, as well as a practicing clinician. He is an affiliate of the Center for Diabetes and Metabolism and the Simpson Querrey Institute for Epigenetics.

He is also a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. Barish has been interested in the BCL6 gene, which encodes a transcription factor, for over a decade, primarily to understand how it can impact diabetes and other endocrine disorders.

The study was published last week in *Nature Metabolism*.

The team used multiple strategies to explore the gene's function, including deleting the gene in utero to see the impact on pre-formed muscle tissue and turning off the gene in adult mice, which caused a rapid loss in muscle mass. The mice born without BCL6 genes were runted and developed muscles that were 30% reduced in mass. Interestingly, even post-development, in adult mice, the gene had a strong impact on the ability to sustain muscle.

"The findings were totally consistent, and it's a robust effect that

suggests a new function for this gene that has principally been studied in the immune system, but it seems to be a very important switch in controlling muscle mass," Barish said.

When muscle mass falls outside of a normal range, it results from a breakdown of the careful balance the body holds between protein synthesis and degradation. When protein synthesis is affected, typically, one step of the protein expression process—transcription or translation—is thrown off balance. However, in the case of BCL6, the scientists found a dual function. Using ribosomal sequencing, they found the gene not only controls transcription, but some of its regulated genes that control translation.

The gene additionally seemed to impact the degradation of proteins. "There's decreased synthesis occurring, and there's more degradation occurring," Barish said. "So between the two, the net effect is muscle mass reduction when BCL6 is lost."

Barish said his study opens up one mechanism to explore in relation to conditions that cause muscle wasting, like nerve injuries, nutrient deficiency, cancer, and immobility, all conditions that lack medical treatments specific to muscle loss. Cancer and nutritional insufficiency result in reductions of BCL6, but more work needs to come to understand how they impact each other.

Loss of muscle mass is associated with worsening diabetes and insulin resistance, and one of the reasons people get more insulin resistant and more diabetic as they age is they lose muscle mass.

People who lose muscle mass also become weak with aging and more susceptible to falls and fractures that land them with an orthopedist.

Muscle mass has a direct impact on other disease states, quality of life,

and morbidity and mortality, yet therapeutics for muscle loss do not exist. Barish said there remains much to understand about how muscle mass is controlled on the molecular level that his approaches are beginning to open doors to.

More information: Krithika Ramachandran et al, Transcriptional programming of translation by BCL6 controls skeletal muscle proteostasis, *Nature Metabolism* (2024). DOI: 10.1038/s42255-024-00983-3

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